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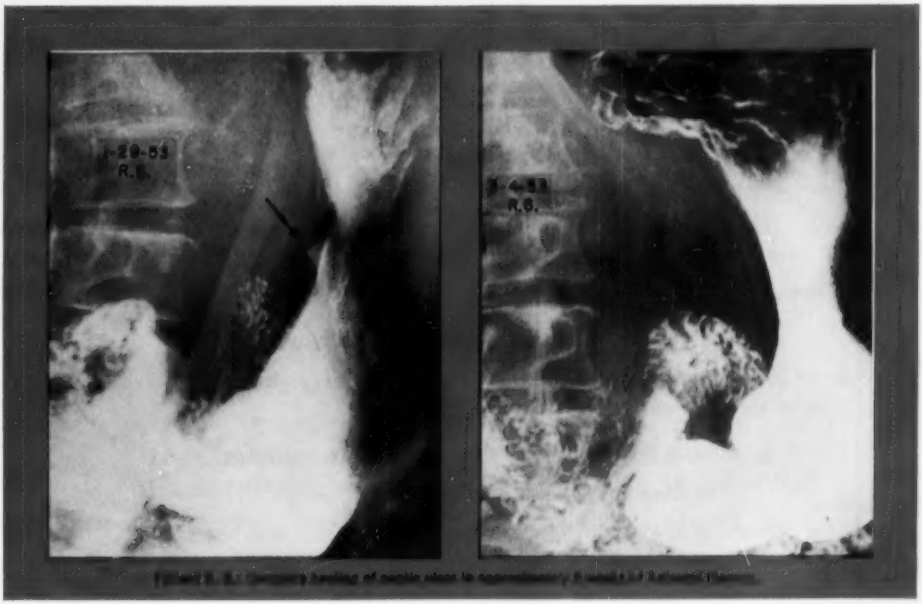

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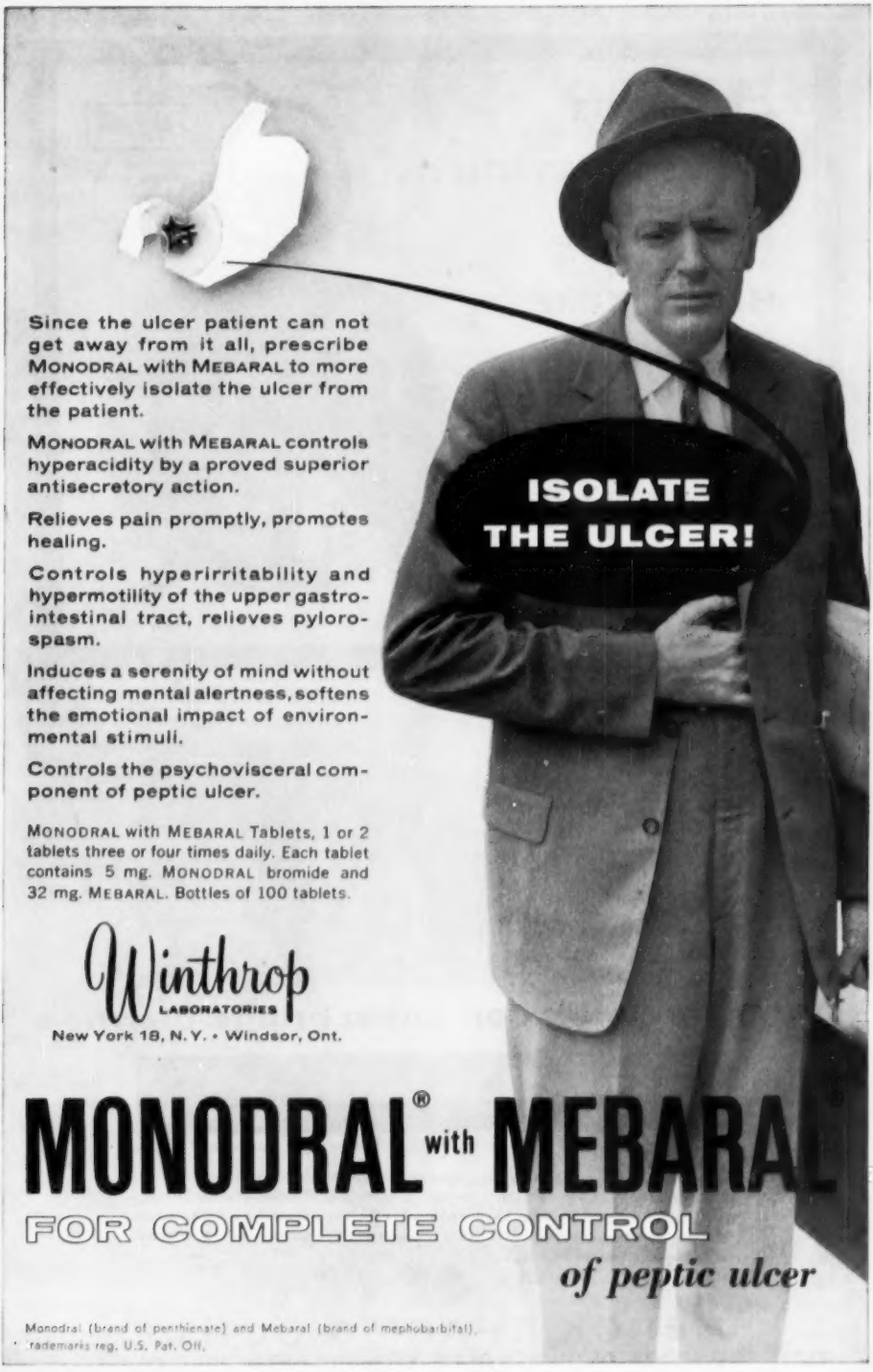

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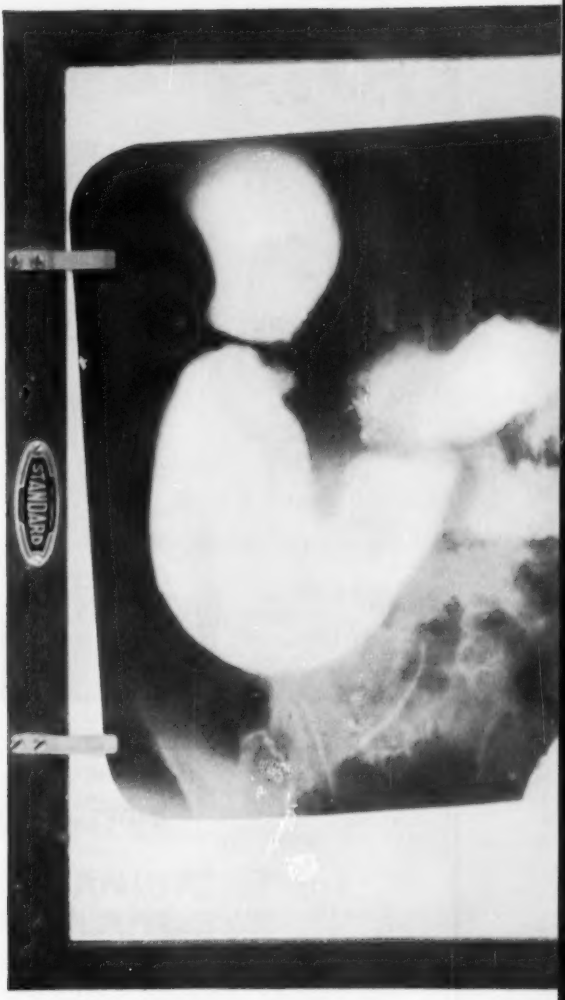

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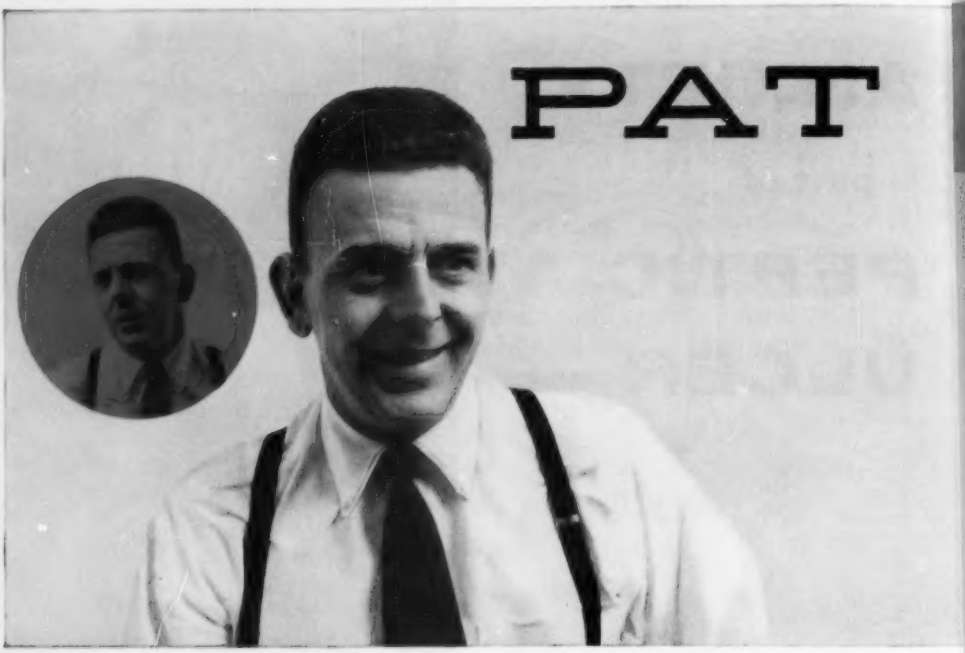

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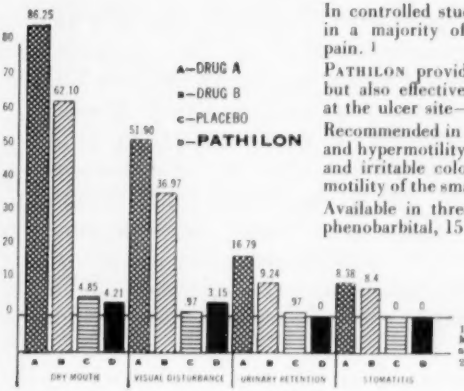

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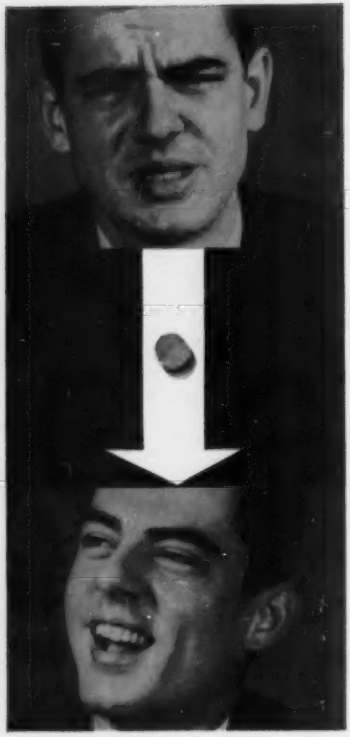

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Chronic (Noncirrhotic) Diffuse Liver Disease

Clinical Studies with Special Reference to Esophageal Varices and Hemorrhage

EDDY D. PALMER, LT. COL. (MC) U.S. ARMY

WHEN PORTAL HYPERTENSION is considered in connection with diffuse liver disease, it is customary to think only in terms of cirrhosis so that there is danger of overlooking the fact that many other liver diseases are capable of producing intrahepatic portal obstruction and, therefore, esophageal varices. One of the difficulties encountered in thinking about this matter is that the element in diffuse liver disease which is believed to be responsible for venous block is the regenerating lobule, and lobular regeneration occurs late in the histopathologic progression to cirrhosis. The noncirrhotic liver diseases which are capable of producing portal hypertension are accompanied by no more than an insignificant amount of lobular regeneration, if any. Whatever the explanation for the altered venous dynamics may be, the fact remains that some of these other diseases are often associated with varices, and these varices sometimes cause important bleeding.

This report deals with a group of chronic noncirrhotic liver diseases which are characterized by rather minor subjective manifestations, a large liver, little interference with hepatic activity as judged by the liver-function tests, and "nonspecific" hepatic histopathologic changes.

From the Gastroenterology Service, Walter Reed Army Hospital, Washington, D. C. Present address: 2nd General Hospital, APO 180, New York, N. Y.

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These are the diseases which are often referred to by the admitted misnomer "chronic hepatitis."

MATERIAL AND METHOD

The 67 patients reported upon were selected because of the liver-biopsy finding of diffuse chronic noncirrhotic liver disease. Although diseased liver tissue is likely to demonstrate a great many different abnormalities which are minute but important, it will be best understood what diseases were represented if it is simply stated that the main histopathologic abnormality in 24 of the patients was portal fibrosis without perilobular fibrosis; in 21, extensive fatty metamorphosis; in 10, portal fibrosis plus prominent round-cell infiltration of the portal areas; in 8, portal fibrosis plus a significant degree of fatty metamorphosis; and in 4, simply prominent round-cell infiltration of the portal areas. The patients were all Caucasian men except for 7 Negroes—6 women and 1 man. The numbers of patients per age-decade, from the second through the seventh decades, were, respectively, 4, 15, 19, 18, 6, and 5.

These were hospitalized patients, personally studied. Many were later followed as outpatients and rehospitalized as it seemed desirable. In addition to the usual bedside observations, liver-function tests, and liver biopsy, the patients were studied with special reference to portal hypertension. Esophageal varices were sought in all by contrast fluoroscopy and by esophagoscopic examination under 4-diameter telescopic magnification (Eder-Hufford esophagoscope). When varices were encountered, they were classified according to the linear extent of the esophagus over which they coursed and the diameter of the majority of varices in the segment where they were largest. The latter was recorded as mild when this diameter was by direct measurement less than 3 mm., moderate when it was between 3 and 6 mm., and severe when it was more than 6 mm. An effort was usually made to measure the portal venous pressure by needle puncture of the varices and direct manometry; however, because in many cases the diameter of the varices was very small, valid readings were obtained in only 7 instances.

CLINICAL FEATURES

The circumstances which led to recognition of the existence of illness in each of the patients are shown in Table 1. In only a small number was the liver disease of any subjective consequence, and, if it had not been for the presence of unrelated disease and the Army's routine

TABLE 1. Circumstance Leading to Medical Study

	No. patients
Illness other than hepatic	33
Routine physical examination	13
Sudden hematemesis	11
Right upper abdominal pain	6
Weight loss, dyspepsia, fatigue	4

TABLE 2. Incidence of Factors Possibly Significant as the Explanation for the Observed Liver Disease

	No. patients
Chronic alcoholism	26
Chronic alcoholism plus past viral hepatitis	5
Viral hepatitis, 2½ to 15 years previously	18
Postvaccinal hepatitis, 9 to 13 years previously	3
"Recurrent hepatitis," not well substantiated	2
Recurrent viral hepatitis	1
POW for 18 months, 3 years previously	1
None evident	11

annual physical examination, most of the cases would have passed unnoticed for the time being. Although 11 of the patients first came to medical attention because of hematemesis, in only 5 of these was the liver disease, through esophageal varices, responsible.

In a review of the patients' past histories to find possible bases for the liver disease, chronic alcoholism was found to be the most common likely factor (Table 2). Twenty-nine of the patients gave a history of viral hepatitis, three following yellow-fever vaccination at the beginning of World War II. Unfortunately, their vaccine lot-numbers were not determinable. The question of recurrent viral hepatitis was raised by two of the histories and seemed satisfactorily proved in a third. Another patient had undergone 18 months of severe starvation as a prisoner of war three years prior to his study.

The physical common denominator that occasioned suspicion of liver disease during routine physical examination of the asymptomatic patients and during care of those sick with other diseases was hepatomegaly. It was present in all of the patients. It was not severe in any instance, the liver edge in most cases descending between 3 and 6 cm. below the costal margin in the right nipple line during inspiration.

Splenomegaly of mild degree was found in 11 patients. Surprisingly, spider angiomas were present in 13, never of large size or great numbers but with all the features that one might expect in frank cirrhosis.

No jaundice, palmar erythema, distended abdominal veins, venous stars, ascites, or edema was observed in this group.

Other gastrointestinal diseases were fairly common: duodenal ulcer in 12 patients, gastric ulcer in 3, hiatus hernia in 4, and esophageal diverticulum, cholecystolithiasis, erosive esophagitis, and chronic pancreatitis with calcification in one patient each. The incidence of ulcer (22 per cent) was significantly high, reminiscent of its increased incidence in portal cirrhosis.

HEMORRHAGE

Twenty of the 67 patients were either hospitalized because of hematemesis or gave a history of hematemesis prior to study, and four others described stool color in the past which was interpreted as indicative of melena. The opportunity presented itself for investigation of the source of bleeding during active upper gastrointestinal hemorrhage in 11 cases. By esophagogastroscopy it was proved that the blood was issuing from esophageal varices in 5 patients and not from varices in the rest. Because 5 of the patients who were not examined during active bleeding gave a history of repeated small hemorrhages but had no varices at the time of the present study, it was considered quite certain that 11 of the 20 bleeders had bled from sources other than esophageal varices.

There were no deaths from bleeding in this series. Among the 9 patients in whom esophageal varices were either the proved or suspected source of bleeding, 4 had had repeated small bleedings; 3, a single moderate hemorrhage; and 1 each, a single small and a single severe hemorrhage.

The other sources of hemorrhage were proved in 6 instances: gastric ulcer 3 times, duodenal ulcer twice, and erosive esophagitis unattended by varices once. Duodenal ulcer was the probable source in the remaining 5 patients.

ESOPHAGEAL VARICES

Esophageal varices were found in 24 of the 67 patients. In only one of these was the radiologist successful in demonstrating the lesions. Eighteen of the affected patients were examined gastroscopically, but gastric varices were found in none. In comparing the incidence of esophageal varices with the other physical findings, it was observed that 4 of the 11 patients with splenomegaly and 7 of the 13 with spider angiomas had varices.

TABLE 3. Chief Histopathologic Features Correlated with Incidence of Varices

	No. patients	No. with varices
Portal fibrosis	24	11
Fatty metamorphosis	21	6
Portal fibrosis and fatty metamorphosis	8	3
Portal infiltration	4	2
Portal fibrosis and infiltration	10	2

Table 3 shows the correlation between the presence of varices and the dominant abnormal liver-biopsy finding. It is seen that none of the structural changes proved innocuous as far as varices were concerned, nor did any seem notably more prone to produce varices. It could only be assumed that the severity and perhaps duration of the process, not the quality, were the significant factors.

The severity of the varices as observed at the first esophagoscopic examination was classed as mild or moderate in all but one patient, an unusual instance in which the entire esophagus was involved by severe varices. In only 5 patients was more than the distal one third of the esophagus affected. The seven portal venous pressure measurements believed to be valid gave readings which ranged considerably below those which might be expected in a group of cirrhotic patients: 120, 200, 230, 280, 290, 290, and 360 mm. of water.

Fourteen of the patients with varices were examined esophagoscopically more than once, and the results are given in Table 4. In three instances the second examination, after intervals of 6 weeks, 6 weeks, and 3½ years, respectively, showed varices where none had existed before, and in three others varices disappeared at least temporarily as time passed. In the other patients the varices got better or worse, or remained unchanged in a random fashion. No correlation could be found between changes in the severity of varices and changes in the other evidences of liver disease or of portal hypertension, such as hepatomegaly and splenomegaly.

DISCUSSION

It has not been the intent of this presentation to enter the controversy over the significance and interrelationships of the different histopathologic forms of liver disease which were encountered among the patients, nor has it been the intent to ignore the degree of histopathologic heterogeneity represented. To the clinician the specific type and stage of the liver disease being dealt with are, of course, of great importance, particularly for predicting the probable subsequent course

TABLE 4. Course of Varices in 14 Patients Examined Esophagoscopically More Than Once

Pt.	Histopathology	First exam.	Interval (wk.)	Second exam.	Interval	Third exam.
1	Portal fibrosis	Mod., 1/3[a]	2	Mod., 1/2[a]	..	..
2	Portal fibrosis	Mod., 1/3	3	Normal	..	..
3	Portal fibrosis	Mod., 2/3	2	Mild, 1/4	..	..
4	Portal fibrosis	Mild, 1/3	2	Mild, 1/3	..	..
5	Portal fibrosis	Mild, 2/3	5	Mild, 1/3	..	..
6	Portal fibrosis	Mod., 1/3	5	Mod., 1/2	..	..
7	Portal fibrosis	Mod., 2/3	14	Mod., 1/2	10 mo.	Normal[a]
8	Fatty metamor.	Mod., 1/3	2	Mod., 1/3	..	..
9	Fatty metamor.	Mild, 1/3	9	Mild, 1/3	..	..
10	Fatty metamor.	Mod., 1/3	11	Mod., 2/3	14 wk.	Mod., 2/3
11	Fatty metamor.	Mild, 1/3	6	Normal	..	..
12	Portal infilt.	Normal	6	Mild, 1/3	6 wk.	Mild, 1/2
13	Portal infilt.	Normal	6	Mild, 1/3	4 wk.	Mild, 1/2
14	Fibrosis and infilt.	Normal	3 1/2 yr.	Mod., 1/2	..	..

[a] Severity as judged by diameter of lesions and proportion of esophagus involved.

of hepatic dysfunction and possible progression to cirrhosis. This is, however, a different matter. The purpose of the present study was to elucidate some manifestations of chronic noncirrhotic liver disease as it itself is encountered, without consideration of possible subsequent histopathologic events.

Taken individually, the patients displayed no clinical features which in any way permitted an accurate prediction of the type of liver disease present. Cirrhosis had been suspected on initial examination in some cases. Because liver biopsy has the familiar frailty of every sampling technic in that it delivers only the tiniest bit of the whole organ for study, biopsy was repeated in many of the patients with the thought that cirrhosis might be revealed by a second specimen.

It is to be noted that the main feature which brought the illnesses to light was hepatomegaly, discovered in most instances by routine examination of people who had no subjective manifestations referable to the liver or to secondary portal hypertension. Portal fibrosis, portal infiltration, and mild degrees of fatty metamorphosis do not invariably produce clinically detectable hepatomegaly, and, therefore, it is highly probable that many mild or early cases were overlooked during the present study because of normal liver size. The importance of unrecognized cases lies in both the probable progression of some of them at a later date to cirrhosis and the danger of hemorrhage from unsuspected esophageal varices.

It is very difficult to speak in precise terms of the incidence of esophageal varices in any form of liver disease, because varices come and go in ways as yet unpredictable. Thus, a second examination in 3 patients of the present group showed varices where none had existed before, even though in two only a short period had elapsed between examinations. There is no question but that repeated examinations of the patients in whom varices were not found would have revealed that varices developed in some from time to time. This vacillating characteristic of varices is to be expected, however far the liver disease has progressed, and it is an important feature of the varices which are secondary to cirrhosis.

The size and extent of the varices observed in the present group, as well as the degree of portal hypertension, were not as severe as those ordinarily encountered in a group of cirrhotic patients. Similarly, the incidence of hemorrhage of proved variceal origin was comparatively low. Nevertheless, hemorrhage was a serious feature of the clinical picture in some cases. If it had not been for esophagoscopic examination

during active hemorrhage, the cause would likely have been ascribed in retrospect to later-detected ulcer in many instances.

The mechanism of portal hypertension and esophageal varices in these forms of liver disease is not clear. It is certain from the histopathology that many of the patients will eventually develop cirrhosis, although it is believed that none had by the time of study. None of the liver biopsy specimens revealed any evidence of lobular regeneration. One can only conclude that the esophageal varices which are encountered in cirrhosis may develop during the precirrhotic stages of the liver disease, and that regenerating liver lobules, although they may aggravate portal hypertension, are not the initial explanation for the development of varices.

CONCLUSIONS

Chronic liver disease which is characterized histopathologically by portal fibrosis, portal round-cell infiltration, and/or fatty metamorphosis, in the absence of the perilobular fibrosis of cirrhosis, is usually a subclinical process, detected by the chance discovery of hepatomegaly. This hepatomegaly was a constant feature of the 67 patients reported upon, but it is highly probable that many other cases have been overlooked during the period of study because there was no liver enlargement. Mild splenomegaly and spider angiomas are not rare in chronic noncirrhotic liver disease.

Esophageal varices are moderately common in patients with these forms of liver disease, but the precise incidence cannot be given because, as in cirrhosis, varices wax and wane and may disappear from time to time. In most instances they are only of mild or moderate size, and this makes radiologic detection impossible in most cases.

Hemorrhage from esophageal varices is not nearly the threat that it is in cirrhosis, yet the risk exists and the ensuing hemorrhage may be severe.

The esophageal varices which are encountered in cirrhosis may have their inception during the precirrhotic stages of chronic liver disease, before the beginning of lobular regeneration.

Serum Calcium Levels in Unrecognized Perforated Peptic Ulcer

Report of Two Cases

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IN TYPICAL CASES of perforated peptic ulcer, the clinical picture is such as to leave little doubt as to the diagnosis. However, where the leak is small or incompletely plugged with omentum, the diagnosis is more difficult. Indeed, in such cases perforated peptic ulcer may be indistinguishable from acute pancreatic necrosis.

The differential diagnosis of acute pancreatitis from other acute abdominal catastrophes is fraught with many well-recognized difficulties. The clinical picture of necrotizing pancreatitis is often similar to that of other acute abdominal lesions. The serum amylase determination, although diagnostically helpful, may be similarly altered in many of these conditions.[1] Moreover, in acute pancreatitis the serum amylase may not be increased, if the examination is delayed beyond the early course of the disease. Therefore, the determination of serum calcium for diagnostic purposes has been increasingly popular in differentiating other acute lesions of the abdomen from acute pancreatitis, particularly since the work of Edmondson *et al.* in 1940.[2] Edmondson and Berne found that in 70 per cent of patients with moderate to severe attacks of acute pancreatitis, the serum calcium level was depressed, usually between the second and fourth day.[3] Therefore, they later suggested that "serum calcium determinations were of diagnostic help in those patients with complete destruction of the pancreas or those seen late in the course of the disease—situations in which the serum amylase and urinary diastase may be normal."

Certainly, in the list of diseases to be differentiated from acute pan-

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creatitis, acute perforated ulcer stands high. We have recently had the opportunity to study two cases of proved acute perforated peptic ulcer in which serum calcium determinations were made and found to be low. The finding of a low serum calcium in the first case was one of the contributing factors to the delay in the application of appropriate therapeutic management. This case was subsequently operated on and a simple closure performed. The other case survived only 12 hours after hospital admission and was examined at postmortem.

CASE 1

C. C. 136390, a 37-year-old white male was admitted on 7/3/56 to the private medical service with the chief complaint of severe pain at the base of the neck. The ensuing history is of doubtful authenticity, because of the physical state of the patient. It was, however, ascertained and later confirmed by members of the family, that he had had episodes of nausea, vomiting, and "indigestion" for a number of years. However, the patient stated that pain or distress had occurred only once previously, about three weeks prior to admission. This preceding episode of pain was associated with vomiting, but no blood was observed in the vomitus by the patient. However, he did believe that his stools were black on two or three occasions, but was unsure of the tarriness of these stools.

On the day prior to admission he felt nauseated and then, suddenly, noted a pain posteriorly at the root of the neck. This pain persisted for the 24 hours prior to admission and seemed to become more diffuse. Vomiting continued for this entire period. Nothing else of note was reported except a fairly heavy alcoholic intake.

Physical examination revealed an acutely ill, young white male, who was cold, clammy, and quite dyspneic. Blood pressure 80/60, pulse 120 per minute, temperature 102° F., rectally, and respiration 30 per minute. Findings in the head and neck were essentially negative; there was questionable nuchal rigidity. Examination of the chest revealed only scattered rales posteriorly over the lung bases. The heart was negative to all modalities of physical examination. The abdomen was moderately tense and was definitely tender in both upper quadrants, the left perhaps more so than the right. Peristalsis was absent. It was noted that pressure over the upper abdomen produced increased pain in the neck. The abdomen was neither distended nor rigid, and no organs were enlarged or palpated.The neurologic examination was within normal limits. Stool obtained on the gloved finger was strongly positive for occult blood.

In laboratory examinations on the day of admission, the hemoglobin was 15.5 Gm. per 100 cc. blood, hematocrit was 55 per cent, WBC 23,000 per cu. mm. Plane film of the abdomen revealed only generalized hazziness "suggestive of ascites." The chest film showed no air under the diaphragm, but the

diaphragm was elevated. Lumbar puncture was negative. On the fourth day of his illness, the serum amylase was 215 units. The serum calcium was 6.4 mg./100 cc. serum sodium 151.4 mEq., serum potassium 6.4 mEq., CO_2 14.5 mEq., chlorides 102.0 mEq., blood sugar 73 mg./100 cc., and blood urea nitrogen 4.1 mg./100 cc. There were nonspecific changes in the electrocardiogram. The patient was treated during this period with solutions to correct electrolyte imbalance, with nasal suction, and with norepinephrine to maintain blood pressure.

On the ninth hospital day the patient's condition had improved to such a degree that it was considered that he could withstand an exploratory laparotomy.

At operation a generalized peritonitis and a partially sealed-off acute perforated duodenal ulcer was found. The ulcer was closed. Recovery ensued after a stormy post-operative phase.

CASE 2

S. W., 111657, a 59-year-old white female was admitted on 2/6/55 with the chief complaint of acute right lower quadrant abdominal pain. The patient had been treated for biliary disease for several years by her family doctor. This consisted of right upper quadrant distention, nausea, vomiting, flatulence, and eructation, especially after the ingestion of fried and fatty foods. There had never been any pain or colic. For several days prior to admission the patient had been experiencing these same symptoms. Shortly after arising on the day of admission the patient experienced an acute, stabbing pain in the right lower quadrant of her abdomen. This lasted approximately 15 minutes and disappeared spontaneously. She was seen by her family doctor who treated her for an attack of acute cholecystitis and she remained comfortably in bed until that afternoon. During the late afternoon she became markedly short of breath and finally cyanotic. She was brought to the accident ward and admitted in a state of peripheral vascular collapse.

Physical examination on admission revealed an elderly white female in acute respiratory distress. Blood pressure was 0/0, pulse 120, weak, and thready, respiration 30 per minute, and temperature 100 F., rectally. Examination of the head and neck was within normal limits except for moderate mottled cyanosis. The lungs were clear to auscultation and percussion; the heart was not enlarged, there were no murmurs, and the rhythm was normal at a rate of 120 per minute. Examination of the abdomen revealed slight tenderness in the right lower quadrant, but no muscle guarding or rebound tenderness. The liver, kidneys, and spleen were normal and there were no abnormal masses palpated. Rectal examination revealed no organic abnormalities, but the rectum was filled with black stools which tested 4 plus for occult blood. Neurologic examination was within normal limits. The patient was treated with intravenous fluids, gelatin, and blood, and her blood pressure rose to nearly normal levels.

Hemoglobin and WBC done shortly after admission were 15.0 Gm./100 cc. and 3450 per cu. mm., respectively. Electrocardiogram revealed nonspecific ST segment and T wave changes. The patient's condition remained about the same throughout the night. The following morning her BUN was 47 mg./100 cc., blood sugar 214 mg./100 cc. (recent infusion of glucose), serum amylase 135 units, and serum calcium 6.9 mg./100 cc. There was no change in her hemoglobin or WBC. At this time it was noted that her abdomen was slightly distended and that there was a grayish-blue mottled cyanosis in the periumbilical region. The patient then underwent a rapidly progressive downhill course and died.

Postmortem examination revealed an acute perforated ulcer of the anterior wall of the duodenum along with a chronic ulcer of the posterior wall of the duodenum. The only change noted in the pancreas was that of mild hyperemia, and this can probably be attributed to the prolonged state of peripheral vascular collapse, as similar changes were noted in the liver, spleen, kidneys and lungs. The gallbladder was normal.

SUMMARY AND DISCUSSION

The use of serum calcium determinations as a diagnostic measure has been suggested, particularly when the serum amylase level is normal. The lowest serum calcium values are usually found between the second and fourth days of an attack of acute pancreatitis.[2]

Two cases of perforated peptic ulcer have been presented in which hypocalcemia was present and, therefore, was not of diagnostic help. These values were found on the fourth and second days of the illness, respectively.

The mechanisms by which the serum calcium is depressed in acute pancreatitis are not clearly understood.[4] The possibility exists that mechanisms other than the mobilization of calcium in the areas of fat necrosis, as suggested in the older literature, play a role.[5] The excretion of calcium into the small intestine is elevated in the presence of excessive stimulation of the adrenals by corticotrophin.[6] Moreover, the presence of nasal suction, commonly used in various acute abdominal emergencies, will further account for low serum calcium values.[3]

Since perforated ulcers are usually recognized early in the course of the disease and appropriate therapy is instituted, the serum calcium level is not routinely determined. This accounts for the lack of previous recognition of this correlation. It is suggestive, at least, that some factors common to both necrotizing pancreatitis and perforated ulcer are operative in depressing the serum calcium levels. Whether or not the hypocalcemia is a result of biologic stress remains to be proved.

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ADDENDUM

Since completion of this report our attention has been directed to Case Report 42352 of the Massachusetts General Hospital, appearing in the *New England Journal of Medicine* (*255:* 441, August, 1956). In this report calcium values of 4.0 and 4.4 mg. 100 cc. were observed in a case of another type of intra-abdominal catastrophe—gangrenous small bowel due to obstruction produced by an adhesive band. The attending physicians likewise in this case suspected acute hemorrhagic pancreatitis because of the hypocalcemia.

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Massive Pneumoperitoneum and Pneumoretroperitoneum After Gastroscopy

Report of a Case and Review of the Literature

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GASTROSCOPISTS HAVE STUDIED the relative risk of gastroscopy by questionnaire[14, 21] and by screening individual series in the compilation of excellent reviews.[13, 21] The serious complications of gastroscopy have consisted principally of perforation of the pharynx and esophagus. Perforation of the stomach seems to be relatively innocuous. The incidence of perforations and their locations are summarized in Table 1. There is some duplication of cases in these reports. Consequently, the perforation of the jejunum reported by Rumball[24] is noted in three of the tabulations, as are the collected cases from several large published series.[1, 9, 11, 21, 22, 23, 25, 28]

It appears that the risk of perforation in flexible gastroscopy is approximately 1 in 1000 examinations. This figure may be exaggerated, since many reports were submitted after a perforation occurred and only the examinations to the time of perforation were reviewed. However, it will be seen that several of the gastric perforations were asymptomatic and discovered by chance, suggesting that some gastric perforations may go unnoticed.

Perforation of the pharynx or esophagus is a catastrophe requiring immediate surgical intervention. Perforation of the stomach rarely requires intervention unless signs of peritonitis develop: it has been termed a remarkably benign accident by Palmer.[21] A review of the

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TABLE 1. Incidence of Gastroscopic Perforations

Authors	Year	No. exams	Perf. of pharynx or esophagus	Perf. of stomach	Other sites	% perforation
Schindler[37]	1940	22351	1 (1)[a]	8 (0)	1[b] (0)	.044
Jones *et al.*[14]	1951	49000	50 (21)	9 (1)	0	.119
Palmer[21]	1954	25077	17 (8)	9 (0)	1[b] (0)	.108
Hunter[13]	1955	29986	14 (7)	17 (1)	1[b] (0)	.110

[a] Figures in parentheses show mortality.
[b] Rumball's[24] case.

published cases of perforation tends to confirm this view. On occasion[4, 7, 8, 11, 15, 29, 35] laparotomy immediately after a supposed perforation has revealed no gastric tear. Most cases of perforation diagnosed on the basis of free air in the peritoneal cavity have been treated conservatively.[1, 2, 12, 16, 19, 23, 26, 33, 34] Indeed the gastric perforations which have been detectable as rents in the stomach wall at surgery have been rare.[1, 25, 35]

It is the purpose of this report to present a case of pneumoperitoneum, pneumoretroperitoneum, and pneumomediastinum detected following gastroscopy, to review the literature, and to discuss the mechanism of production of the roentgenographic findings. This case represents the first recognized perforation in 1314 gastroscopies and 221 flexible esophagoscopies performed on this service.

CASE REPORT

F.M., a 62-year-old white, male laborer, was admitted to the Pulmonary Disease Service of the West Haven VA Hospital on September 9, 1955, because of hemoptysis. A chest film taken prior to admission was suggestive of tuberculosis. The only symptom related to tuberculosis was fatigue. The patient complained of "heartburn" all of his adult life. Two weeks prior to admission he developed a sore tongue. There were no additional gastrointestinal symptoms.

Physical examination revealed a markedly cachectic, pale, white male who appeared chronically ill. Rectal temperature was 100.8° F. Cheilosis was noted. The tongue was beefy red and smooth and had papillae only at the borders. The trachea was deviated to the right of the midline. Mild dorsal kyphosis was present. Changes on percussion and many rales were noted over both lung fields. Deep tendon reflexes and vibratory sense were normal. The remainder of the physical examination was not significant.

The positive laboratory findings included a hemoglobin of 9.5 Gm. and hematocrit of 32 per cent, achlorhydria both before and after histamine stimulation, stools slightly positive (guaiac test) for occult blood, and sputum positive for acid-fast bacilli.

Fig. 1. View of the stomach demonstrating lesser curvature irregularity. *Fig. 2.* Upright roentgenogram demonstrating far-advanced tuberculosis and massive pneumoperitoneum.

Fig. 3. Pneumoretroperitoneum with both kidneys shown. The left kidney is atrophic. *Fig. 4.* Upright lateral chest film demonstrating free air under the diaphragm. Air is also seen about the aorta (*arrows*) in the mediastinum.

Roentgenograms of the chest revealed bilateral cavitation and far-advanced tuberculosis. On September 13, 1955, barium enema disclosed diverticulosis of the sigmoid. A gastrointestinal series on September 21, 1955, revealed a defect along the lesser curvature of the stomach (Fig. 1.). The radiologist commented that "despite the normal appearance of the stomach, [I] would suggest gastroscopic exam to be sure no abnormality is present on direct visualization."

Gastroscopic Examination

On September 28, 1955, a gastroscopic examination was undertaken. The patient was prepared with sodium phenobarbital 100 mg. intramuscularly, morphine sulfate 10 mg. subcutaneously, and atropine sulfate 0.4 mg. subcutaneously. The pharynx was anesthetized with 8 cc. of 1% Benadryl solution (p.o.) according to the method described by Selesnick[31] and used routinely on this service. Gastric aspiration was not done.

The Eder-Chamberlin gastroscope was introduced with ease and passed to the cardia where some resistance was encountered. After a short pause, gentle pressure was exerted and the instrument passed into the stomach. A small initial amount of air was instilled. A round view of the stomach could not be obtained. It seemed as if a whitish-pink membrane was covering one third of the objective, in half-moon fashion, from the patient's right. This field defect persisted. In the remaining two thirds of the field, atrophic mucosa, with vascularization, was noted. The stomach was never expanded fully with introduction of air, yet the patient did not belch. The instrument could not be advanced further than the proximal pars media. A second observer (S.S.) confirmed these findings. On withdrawal the instrument seemed to be held up at the cardia. After a brief delay it was withdrawn easily. The entire examination had taken 5 minutes.

The patient had experienced no pain and, except for an inability to belch, felt well. He returned to his ward and ate supper. At 9:00 P.M., 7 hours after the examination, the patient complained of a feeling of distention and, again, of an inability to belch. He was afebrile and his vital signs were stable. The abdomen was markedly distended and liver dullness was obliterated. A tympanitic percussion note was detectable in all quadrants. There was no tenderness. There was no subcutaneous emphysema or mediastinal crunch.

A Levin tube was passed and a small amount of curdled milk removed. The patient felt comfortable immediately and commented that his feeling of distension had been relieved. Roentgenograms (Figs. 2 and 3) revealed massive pneumoperitoneum and pneumoretroperitoneum. Some air was also detected about the aorta in the mediastinum (Fig. 4.).

Penicillin and streptomycin were started. Because the patient had no discomfort needle aspiration of the pneumoperitoneum was not attempted. The Levin tube was kept in place for 5 days. On the sixth day Lipiodol study revealed no perforation of the esophagus and the patient was again fed orally.

There had been no febrile response and, except for a transient leukocytosis of 14,000 white blood cells/cu. cm. on the day after gastroscopy, the course was benign. Antibiotics were stopped after 6 days. Distention of the abdomen was not clinically detectable 7 days after gastroscopy. However, a roentgenogram on November 2, 35 days after perforation, revealed a small residual amount of subdiaphragmatic air.

DISCUSSION

Pneumoperitoneum as a complication of gastroscopy has been reported seventeen times[1, 3, 4, 5, 7, 8, 11, 15, 18, 19, 23, 26, 29, 33, 34, 35] The exact mechanism of its production remains unproved. It seems probable that except for the rare case[1, 5, 25] there is no actual tear in the wall of the stomach. Various fascinating possibilities have been discussed. A review of the findings of several cases may present a dynamic view of the actual occurrences.

Myhre and Wilson[18] studied 119 patients by roentgenography 24 hours after gastroscopy, in the erect posteroanterior position. All were asymptomatic. In two instances they discovered a line of decreased density around the gastric air bubble which they interpreted as evidence of interstitial gastric emphysema. If this study represents the usual situation, the actual incidence of this phenomenon may be on the order of 2 per cent of all gastroscopies. Apparently no further progress of air occurs in the ordinary case, for proved pneumoperitoneum is rare, and the presence of only 5 cc. of air in the abdominal cavity may be detected roentgenographically.[20] No other studies of this type have been undertaken.

There have been various explanations of the mechanism of introduction of air through the gastric mucosa. Apparently interstitial gastric emphysema need not be a step in the formation of pneumoperitoneum. In Schindler's case[29] no pathology could be detected at surgery. He postulated that air introduced into the stomach had caused a rent through all layers of the stomach wall. The rent had quickly closed, he thought. Chamberlin,[7] after a review of microscopic sections obtained at surgery, suggested that air had been forced into the perineural lymphatics, since these were dilated. His patient had an ulcer and the possibility that air had passed through the bed of the ulcer was mentioned. Fierst *et al.*,[8] whose patient had a malignant ulcer, suggested that air might have passed through the ulcer and then along perivascular sheaths. One patient of the two presented by Asher and Cohen[1], who had a malignancy on the posterior wall, developed pneumoperitoneum. It has been shown that air may pass through normal mucous membranes without overt tears. Brown and Fine[6] recorded a case of diffuse

interstitial emphysema after a double contrast enema, when no perforation of the rectal wall was detected. Air had passed into and through the rectal wall to the retroperitoneal space in large amounts, there being no residual tear apparent on careful examination.

It would seem that one other mechanism by which air might be introduced should be mentioned. In five previous case reports and in the one presented here, some difficulty was encountered negotiating the cardia. An esophageal tear at the cardia on the lesser curvature side would permit air to be introduced both into the peritoneal cavity and retroperitoneally. In the case presented, the half-moon-shaped membrane covering the third of the field on the patient's right would have been in the correct position for such a tear. Franklin,[10] however, mentions only one recorded case of an esophageal tear opening into the peritoneum or peritoneal cavity. The usual course of esophageal perforation is not benign even at the esophagocardiac junction.[32]

Once air has found its way into the wall of the stomach its path can be traced. At surgery Chamberlin[7] described emphysematous blebs along the lesser curvature of the stomach. Air had also progressed within the greater and lesser omentum, as it had in the cases of Gilbert *et al.*,[11] Fierst *et al.*,[8] and Ylvisaker and Myhre.[35] Rents were noted in the omentum, explaining the ultimate pathway by which air reached the peritoneal cavity. In Chamberlin's case the air had also dissected through the gastrohepatic ligament and was found in the aortic sheath. By this route it traveled retroperitoneally and then into the mediastinum. The route detailed confirms the experimental work of Macklin,[16] who working with cats demonstrated this course from above downward. Pneumoperitoneum is seen in therapeutic pneumothorax[17] as is pneumomediastinum in therapeutic pneumoperitoneum,[2] the air passing over the same routes postulated in this case. Pneumoperitoneum may also occur spontaneously after the rupture of an emphysematous bulla of the lung.[12]

Unless signs of peritoneal irritation occur, therapy of pneumoperitoneum after gastroscopy is conservative.[21] Bergh *et al.*[3] and Schindler[30] mention the relative danger of gastric perforations in patients with achlorhydria. Schindler stressed the advisability of surgery for pneumoperitoneum in achlorhydria. The patient here did well in spite of achlorhydria. The mechanism of the perforation with the absence of an overt tear and no peritoneal soilage would explain the benign course and the advisability of conservative therapy. Rappaport and Finkel[23] and Palmer[21] suggest aspiration of the peritoneal air. Unless there is symptomatology related to the pneumoperitoneum, this measure seems un-

warranted since absorption is inevitable. The case reported by Rappaport and Finkel was in extremis prior to aspiration, but responded immediately upon removal of air. Gastric aspiration for five days has been suggested[21] but cases have done well without this therapy.[1, 3, 34] Antibiotics are indicated as a prophylactic measure. The prognosis in pneumoperitoneum after gastroscopy is excellent.

SUMMARY

1. The risk of perforation in flexible gastroscopy has been reviewed.

2. A case of pneumoperitoneum, pneumoretroperitoneum, and pneumomediastinum occurring after gastroscopy has been reported. Treatment was conservative and the course benign.

3. A review of the cases of pneumoperitoneum in the literature and the probable mechanism of their production has been presented. An additional possible etiologic factor of tear at the esophagogastric junction has been suggested.

4. Treatment of the condition has been discussed. Achlorhydria is not considered a contraindication to conservative therapy.

5. The prognosis of pneumoperitoneum after gastroscopy, treated conservatively, is excellent.

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Reserpine in Peptic Ulcer

ERNST J. DRENICK, M.D.

PATIENTS WITH PEPTIC ULCERS are usually tense or emotionally unstable.[1] Therefore, sedatives have often been a desirable therapeutic adjunct in the routine treatment of ulcers. The disadvantages of habituating a patient to sedatives have deterred physicians from their prolonged use. The tranquilizing effect of reserpine,[2] an alkaloid of *Rauwolfia serpentina*, would seem to offer the desired effect without danger of tolerance or addiction. The reason that it has not been recommended in the treatment of peptic ulcers is the possible stimulating effect on the gastric mucosa. It has been shown that parenteral administration of reserpine in dogs produces a marked increase in gastrointestinal secretory and motor activity.[3] Intravenous injection of reserpine in the human evoked a prompt increase in secretion of hydrochloric acid.[4, 5] However, prolonged oral administration to large numbers of mental patients has not been reported to have increased the incidence of peptic ulcers.

The purpose of this brief study was to evaluate the effect of reserpine on gastric acidity in patients with known peptic ulcers, gastritis, or esophagitis. This was done by comparing routine gastric analyses before and during a period of administration of reserpine. Subjective symptoms were recorded and evaluated.

METHOD

Thirteen ambulatory patients ranging from 51 to 72 years were selected for this study. Seven had duodenal ulcers, 3 had prepyloric ulcers, 2 had peptic esophagitis with ulceration, and 1 had gastritis. The diagnosis was established by clinical evidence, x-rays of the upper gastrointestinal tract, and endoscopy. All patients had been on a bland diet. Eight had been on a casual regimen of antacids and 1 had been on antacids and anticholinergic medication before they were included in this study. The dosage had been less than adequate in every case

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and no improvement had occurred over a number of weeks. No changes were recommended in either medication or diet.

After a period of observation of two weeks, during which two gastric analyses were carried out in each patient, reserpine* 0.25 mg. three times daily was prescribed. The period of administration lasted an average of thirty days. During this period gastric analyses were done at weekly intervals on a fasting stomach. No medication was given for eight hours preceding the analysis. A routine gastric analysis consisted of six samples aspirated at 15-minute intervals. Whenever the fasting sample was found to contain no free HCl a subcutaneous injection of 0.5 mg. histamine was given to ascertain by a rise in free HCl that the Levin tube was actually within the stomach. These analyses with achlorhydric fasting samples were not used in the comparison.

RESULTS

All patients were able to take the medication without any difficulty. None complained of an increase in the severity of symptoms, and no side effects were noted. While reserpine was administered the following changes in symptoms were noted:

Pain, which was present in all patients initially, was relieved entirely in 4, it persisted in 4 and was somewhat improved in 5 patients. After the drug was stopped, 5 patients returned after a few days voluntarily requesting reinstitution of the medication because they felt better while taking it. One of these had a recurrence of pain, while the other patients never had been pain free.

Nausea had been present in all 13 patients before treatment. Within two weeks after institution of reserpine 9 were free of nausea, 3 were not improved, and 1, a patient with esophagitis, continued to have nausea for eight weeks.

Vomiting was present in 9 patients before treatment and subsided within one to two weeks in 7 patients. It subsided after eight weeks in 1 patient with esophagitis, and was partially improved in 1 patient after eight weeks. Occult blood in the stools, as shown by the guaiac test before institution of treatment, was present in 5 patients. At the end of the observation period the stools of all patients were negative for occult blood.

X-ray follow-up examinations carried out on asymptomatic patients revealed apparent healing in two instances while reserpine was given.

* Used in this study as Serpasil, registered trade name of Ciba Pharmaceutical Products, Inc.

Effect on Free HCl

A total of 89 gastric analyses were carried out in the 13 patients. Thirty-one analyses were performed before reserpine was administered, and among these were eight instances when the first aspirated fasting sample contained no free HCl. Among the 58 analyses carried out while the 13 patients were receiving reserpine, sixteen fasting samples contained no free HCl. This represents an incidence of 25 per cent of achlorhydric fasting specimens among the control analyses as against a 28 per cent incidence for the analyses carried out while the patients were taking reserpine. The difference does not seem to be significant.

Each sample was titrated separately. The units of acid in each sample were added and divided by the number of samples and thus an average acid level was determined. In each patient one average was determined for all the samples while receiving reserpine and the other average for the samples collected during the control periods. The two averages were compared. Thus it was found that of the 13 patients, 6 had a higher average free acid content while receiving reserpine than during the control period and 7 had a lower average acidity (Table 1). The average number of units for those 6 patients with a higher acid content while on reserpine amounted to +5.6 units as compared to the control period. The average for the 7 patients whose acid content while taking reserpine was lower than during the control periods was −5.3. The even distribution on the positive and negative side and the relatively minor differences seemed to indicate that reserpine did not influence the secretion of hydrochloric acid.

TABLE 1. Average Levels of Gastric Hydrochloric Acid

Patient	Diagnosis	Clinical units of HCl		
		Control period	Reserpine	Difference
1	Esophagitis	19	14	−5
2	Prepyloric ulcer	36	29	−7
3	Duodenal ulcer	36	39	+3
4	Duodenal ulcer	42	44	+2
5	Esophagitis	41	45	+4
6	Duodenal ulcer	53	45	−8
7	Duodenal ulcer	31	25	−6
8	Duodenal ulcer	32	36	+4
9	Duodenal ulcer	38	56	+18
10	Gastritis	33	26	−7
11	Prepyloric ulcer	34	31	−3
12	Prepyloric ulcer	37	38	+1
13	Duodenal ulcer	42	39	−3

CONCLUSIONS

Reserpine administered in doses of 0.25 mg. three times daily had no adverse effect in a number of patients with duodenal ulcers, antral ulcers, peptic esophagitis, and gastritis. Reserpine alone does not seem to be adequate for the treatment of peptic ulcers and cannot replace routine ulcer management. This is best demonstrated by the persistence of pain. After this study all patients were given adequate doses of alkali and prompt recovery occurred in 9 out of 13. No delay in healing could be observed.

Reserpine seemed to be beneficial in the control of nausea and vomiting, indicating that perhaps these symptoms are caused at least in part by some central action. One patient with obstructive symptoms and copious, frequent vomiting stopped within two days without any other medication or change in diet. This observation is in keeping with the findings of Gourzis[6] who showed that, in dogs treated with veratrum, emesis and other gastrointestinal side effects could be prevented by reserpine.[5] The drug also seemed to bring about subjective improvement which prompted 5 patients to voluntarily request reinstitution of reserpine after it had been discontinued. Four of these patients had not experienced any pain relief while taking reserpine but the tranquilizing effect seemed desirable.

No increase in secretion of gastric acid could be demonstrated while patients were taking reserpine. If reserpine seems a desirable mode of treatment for any reason the history or presence of a peptic ulcer should not be considered a contraindication to the administration of this drug.

SUMMARY

Reserpine was added to the routine measures in the treatment of peptic lesions of the upper gastrointestinal tract in 13 patients. In addition to its tranquilizing effect it seemed to be beneficial in the relief of nausea and vomiting. It had no deleterious effect on symptoms or course of the disease and it seemed to have no influence on gastric acidity.

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Book Preview

We are privileged to present a series of excerpts from a forthcoming book, *Practical Diagnosis and Treatment of Liver Disease*, by Carroll M. Leevy, M.D., to be published by Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers. We wish to acknowledge our appreciation of the cooperation and help that Dr. Leevy has extended in the preparation of portions of his book for "Previews."—THE EDITORS.

Clinical Diagnosis of Liver Disease

II. Circulatory Involvement, Fluid Imbalance, and Mental Changes

CARROLL M. LEEVY, M.D.

Collateral Portal Circulation

Collateral circulation develops in patients with intrahepatic abnormalities which interfere with blood flow through the liver. Collateral vessels develop in the abdominal, esophageal, hemorrhoidal, and retroperitoneal areas to facilitate the return of blood to the right heart. Clinical detection of the common collaterals is possible by inspection and auscultation over the upper abdomen; esophagram or esophagoscopy; and anoscopy or proctoscopy.

Blood normally reaches the liver by way of the portal vein and hepatic artery, and is dispersed through interlobular branches. These vessels communicate with the sinusoids and lead to central veins which drain into hepatic veins. An increase in portal blood pressure is responsible for collateral channels. Portal pressure may reach 250 to 600 mm. of water. Portal hypertension is due to mechanical interference with entry of blood into the liver by fibrous connective tissue or regenerated liver cells.[1] Hypertension of the portal-circuit and abdominal-wall collaterals occurs secondary to extrahepatic phlebitis in the Cruveilhier-Baumgarten syndrome which is characterized by a caput medusae and a murmur and thrill over a patent umbilical vein.[2]

Esophageal Varices

Esophageal varices are the important collaterals requiring treatment. They are usually indicative of portal hypertension but may represent congenital venous anomalies, and have been demonstrated in congestive heart failure, viral hepatitis, and portal fibrosis in the absence of an elevated portal vein pressure.[3, 4] Both portal-vein pressure measured directly and pressure obtained by wedging a catheter into a peripheral hepatic vein are elevated in patients with cirrhosis and esophageal varices.[5] Hematemesis suggests the presence of varices in patients with liver disease, but other causes of gastrointestinal hemorrhage must be excluded. The frequent association of chronic liver disease with peptic ulcer necessitates early differential diagnosis.[6] A clinicopathologic study of 5 patients with nutritional cirrhosis, esophageal varices, and peptic ulcer demonstrates the need for evaluating such patients for hemorrhage from all of these sources.

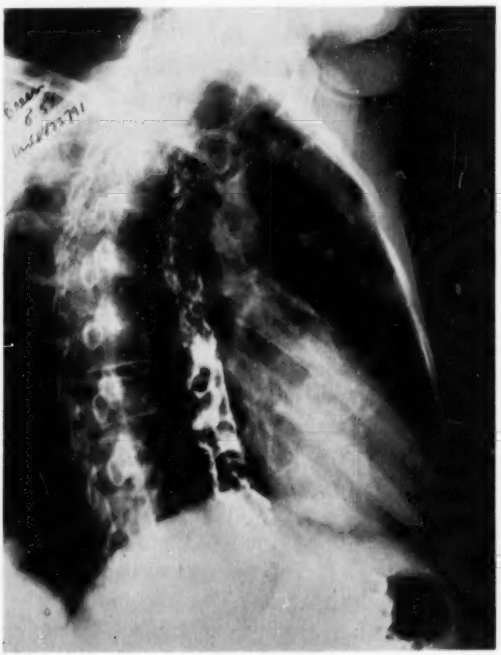

Fig. 1. **Barium swallow demonstrating esophageal varix in patient with asymptomatic nutritional cirrhosis.**

Hemorrhage was attributed to bleeding varices in all of this group; however, 3 patients succumbed to a bleeding duodenal ulcer.

Esophagoscopy is valuable in recognizing esophageal varices. It is a safe procedure, and it is desirable to evaluate all patients with chronic liver disease for the presence of varices by this method. The size of varices, extent of involvement, and condition of the overlying mucous membranes can be studied with esophagoscopy. Varices appear as clusters of soft bluish-gray or red veins. The venous pressure may be measured in varices by a needle-manometer system attached to the esophagoscope.[7] Barium study of the esophagus is a helpful adjunct. A radiologic diagnosis is possible in 60 per cent of cases of esophageal varices if films are obtained when the patient is bearing down while in a horizontal position (Fig. 1).

Splenomegaly

Splenomegaly is an important accompaniment of liver disease. An enlarged spleen may cause symptoms incident to its encroachment on other organs; produce an anemia, thrombocytopenia, and/or neutropenia; or rupture when traumatized. Splenic enlargement in liver disease has been attributed to portal hypertension and passive congestion. Regenerative changes produce an enlarged and fibrotic spleen. Congestion or reticular hyperplasia may be responsible for splenomegaly in instances where the spleen returns to normal with clinical improvement. Peripheral emboli or splenic-vein thrombosis produce splenomegaly in patients with liver disease associated with heart failure. Rarely, carcinomatous metastases to the liver interfere with portal blood flow to cause splenomegaly. An enlarged spleen often disappears with improvement in fatty liver, viral hepatitis, passive congestion, and biliary hepatitis. Splenomegaly usually persists in patients with diffuse hepatic fibrosis, splenic vein thrombosis, and carcinomatous metastases.

Cytopenia

The major adverse effect of an enlarged spleen in liver disease is production of hypersplenic syndromes. Cytopenia is associated with a hyperplastic bone marrow. The peripheral cell type that is reduced is usually increased in the marrow. Two mechanisms have been proposed to explain cytopenia: inhibition of the bone marrow by a humoral factor released from a hyperactive spleen[8]; and selective sequestration and phagocytosis by an abnormal spleen.[9] The first

thesis is supported by the finding of maturation arrest which disappears with splenectomy. The demonstration of a heavy concentration of radioactivity in the spleen and abnormally little activity in the liver following transfusions with Cr^{51}-tagged autogenous red blood cells into patients with cirrhosis and hemolytic anemia suggests that the spleen is the major site of red-cell destruction.

Clinical features depend upon the degree and type of cytopenia. Splenic neutropenia is characterized by recurrent infections, a white blood cell count between 1000 and 3000 per cu. mm., and increased granulocytes in the bone marrow. Splenic thrombocytopenia due to liver disease may be difficult to distinguish from idiopathic thrombocytopenic purpura, although immunologic abnormalities appear to be responsible for the latter condition. In both states there is purpura, a low platelet count, low prothrombin-consumption time, a positive Rumpel-Leede test, decreased clot retraction, and increased megakarocytes in the bone marrow. Splenic anemia is associated with overt or subclinical evidence of hemolysis. There may be an anemia, icterus, reticulocytosis, and marked bone-marrow erythropoiesis; or a lowered red blood cell count and decreased red-cell survival may be the only manifestation of the condition. Splenic pancytopenia is characterized by a combination of the described features of neutropenia, thrombocytopenia, and anemia.

Blood Pressure and Vascular Changes

Current theories of the cause of hypertension and shock all include the liver. It has been demonstrated that experimental renal hypertension is eliminated by hepatic injury. Goldblatt has postulated that hypertension results from the interaction of renin produced in the kidney, and hypertensinogen elaborated in the liver.[10] Shorr proposed that the kidney produces a vasoexcitor substance (VEM) which is opposed by a vasodepressor substance (VDM) manufactured in the muscles and the liver; VEM ordinarily predominates to maintain normal blood pressure levels.[11] Inhibition of the normal hepatic process of deactivation of VDM causes hypotension and shock.

A low incidence of hypertension has been recorded in studies of patients with severe liver disease.[12] Of 250 patients with hepatic cirrhosis due to nutritional deficiency observed in our clinic, 70 per cent had normal blood pressure, 4 per cent had hypotension, and 26 per cent had hypertension. Serial study of 38 hypertensive patients who developed progressive hepatic insufficiency revealed an increase

in hypertension in 5 (13.1 per cent), decrease in 19 (50 per cent), no change in 8 (21.0 per cent), and marked fluctuations in 6 (15.7 per cent). The following case history is illustrative of the decrease in blood pressure which occurred with severe hepatic damage in one half of our hypertensive patients:

Case 1

W.C., a 64-year-old laborer, had documented hypertensive heart disease for ten years, with blood pressure ranging between 180/110 and 196/140, associated with an enlarged heart, retinopathy, and renal dysfunction.

He developed biliary cirrhosis as a result of prolonged common-duct obstruction, and serial recordings showed a gradual reduction of his blood pressure to a level of 120/80. At abdominal exploration, gallstones were found to be responsible for biliary obstruction. The liver was green, firm, and finely nodular. Postoperatively, the patient's blood pressure remained within the normal range and cardiomegaly and eyeground changes improved. There was no evidence of myocardial infarction, a cerebrovascular episode, or other specific mechanism to account for reduction in blood pressure.

Comment. The decrease in blood pressure and improvement in clinical stigmata of hypertensive vascular disease noted in this patient was not accompanied by malnutrition and favors the thesis that liver-cell injury may induce hypotension. Improvement in hepatic reserve may be followed by return of blood pressure readings to previous levels. Although jaundice dis-

TABLE 1. Biochemical and Histologic Findings in a Case of Hypertension with Biliary Obstruction

	At Time of Surgery	8 Months Later
Biochemical study		
Serum bilirubin (mg./100 cc.)	6.0	0.8
Alkaline phosphatase (B.U.)	5.5	7.5
Bromsulfalein (%)	...	42.5
Total serum cholesterol (mg./100 cc.)	213.0	253.0
Cholesterol esters (mg./100 cc.)	130.0	162.0
Serum albumin (Gm./100 cc.)	3.1	3.5
Serum globulin (Gm./100 cc.)	4.5	4.8
Cephalin flocculation	3+	3+
Thymol turbidity (units)	5.0	4.5
Prothrombin time	12.8/12.3	15/15
Histologic study		
Fibrosis	2+	2+
Fat	0	0
Regeneration	3+	3+
Bile Stasis	2+	0
Infiltration	2+	1+
Necrosis	0	0
Other	0	0
Pathologic diagnosis	Biliary cirrhosis	Biliary cirrhosis

appeared in this patient, there was little alteration in his biochemical and histologic abnormalities (Table 1).

Relationship Between Atherosclerosis and Liver Disease

There has been considerable interest in the possible relationship of atherosclerosis and liver disease. Some have reported a decreased incidence of atherosclerosis in patients with nutritional cirrhosis and an increase in biliary cirrhosis. A rough correlation has been noted between atherosclerosis and the serum cholesterol, cholesterol phospholipid ratio,[13] and serum lipid fractionation by ultracentrifugation.[14] In our investigations there appears to be no significant decrease in the incidence of atherosclerosis in patients with liver disease. Nine per cent of patients with advanced nutritional cirrhosis studied at autopsy had significant coronary atherosclerosis. Several patients have been observed with classical clinical and electrocardiographic criteria for a diagnosis of myocardial infarction. Serial electrocardiograms and ballistocardiograms in patients with liver disease have occasionally demonstrated evidence of coronary-artery disease which was unsuspected by history and physical examination.

Fluid Retention and Electrolyte Disturbances

Liver dysfunction is accompanied by subclinical or clinical evidence of abnormal fluid retention. Dilution technics demonstrate an increase in total body water by deuterium oxide or antipyrine methods,[15] and expansion of extracellular water by inulin or sucrose methods.[16] There is a variable effect on the intracellular water, calculated as the difference between total body water and extracellular water; and on plasma volume, determined by Evans blue or iodionated serum albumin.[17]

Ascites

Overt manifestations of fluid accumulation include peripheral edema, pulmonary congestion, ascites, and/or hydrothorax. Ascites causes a reduction in breathing reserve and predisposes to pulmonary infection by interfering with ventilation. Ascites is the most frequent, and often the only, clinical evidence of fluid imbalance. Abdominal localization is due to a difference in the rate of inflow and outflow of fluid from the peritoneal cavity. Radioactive tracer studies show an exchange of 40–80 per cent of peritoneal fluid each 24 hours.[18] Entry of fluid into the peritoneal cavity is increased by mechanisms which reduce renal excretion of sodium and water. Outflow of ascitic fluid

is decreased by hypoalbuminemia, lymph stasis, and venous hypertension.

Ascites can be correlated with the severity of liver injury. Thus, in nutritional liver disease, only 5 per cent of patients with fatty liver have ascites, whereas, over 50 per cent of those with diffuse fibrosis have this sign. Abnormal salt and water retention is responsible for clinical ascites, although its mechanism is unknown. There is decreased total bodily excretion of sodium as a result of pituitary-adrenal changes and other factors not yet clarified.[19] Adrenal salt-retaining hormones have been isolated from the urine and serum of such patients.

Total 24-hour urine sodium excretion is sometime only 10 per cent of normal in advanced liver disease. There is frequently an independent decrease in capacity to excrete water which further increases fluid retention and occasionally leads to syndromes of water intoxication. Serum-protein levels, portal hypertension, hepatic venous obstruction, intra-abdominal tension, and lymph stasis are important contributing factors.[20] Any of these mechanisms may individually play a major role in formation or maintenance of ascites. Hypoalbuminemia facilitates fluid accumulation by reduction of colloidal osmotic ressure. Portal hypertension and obstruction of the hepatic venous bed[21] accelerate transudation of plasma filtrate by increasing hydrostatic pressure. Intra-abdominal tension further distorts intravascular pressure relationships, and abnormal lymphatic drainage prevents a return of extravasated fluid to the plasma.

The chemical composition of ascitic fluid depends upon both the degree of lymphatic block and previous fluid loss. Usually ascitic fluid is a clear yellow transudate with a protein content of 0.02–to 0.03 mEq./100 cc. and a sodium content of 150–180 mEq./100 cc. Occasionally ascitic fluid is turbid or milky owing the presence of a lipoprotein complex or fat globules.

Hydrothorax

Patients with liver disease in whom abnormal fluid accumulation is limited to the chest present a problem in diagnosis. Such pleural effusion is often due to inflammatory or neoplastic pulmonary disease. At times, no cause besides hepatic disease can be found, and accumulated fluid disappears with improvement in liver functions. It has been suggested that pleural effusion in these instances results either from passage of fluid from the abdominal cavity, by way of the

lymphatic vessels of the diaphragm, or from intrathoracic exudation of fluid due to an increase in pressure in the azygos vein.[22]

Sodium and Potassium Alterations

Plasma sodium, interstitial sodium, and intracellular sodium tend to be altered in chronic liver disease. Body salt depletion, hemodilution, and shifts of extracellular sodium into the cells all tend to alter normal distribution of this ion. In some instances of fluid retention refractory to therapy, a complete evaluation of body-sodium content and distribution is important. Simultaneous estimation of plasma volume and serum-sodium concentration provides an index to the total circulating sodium (Fig. 2). Circulating sodium is normally 6.0 ± 0.7 per kilogram of body weight, and may vary from a low of 3.0 mEq./Kg. in salt depletion to a high of 13 mEq./Kg. in salt intoxication.

The total circulating sodium may permit differentiation of hyponatremia due to salt depletion from that due to primary water retention when one of these mechanisms is principally responsible for a decrease in concentration of serum sodium. It facilitates recognition of plasma-sodium deficits with normal serum concentration of

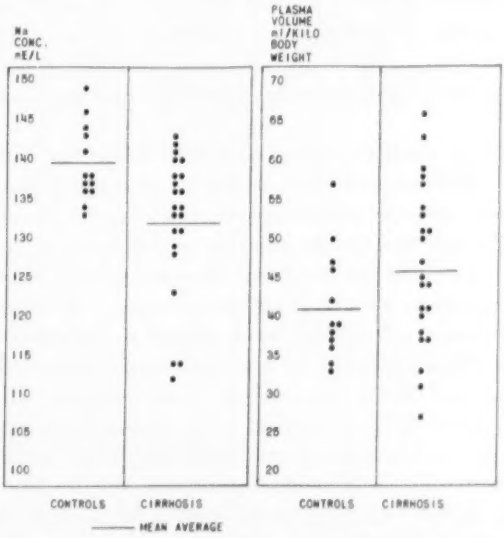

Fig. 2. **Serum-sodium concentrations and plasma-volume studies in nutritional cirrhosis with fluid retention, demonstrating a wide range of values.**

this ion. Determination of total circulating sodium is a practical procedure readily available in most hospitals.[23] Extracellular sodium is determined by a combination of inulin and serum-sodium study; intracellular sodium is derived by subtracting extracellular sodium from total exchangeable sodium measured by Na^{24} dilution.[24]

Similar alterations in body potassium are noted in hepatic insufficiency. A reduction in serum potassium occurs with plasma dilution, excess potassium losses in the stool or urine, acid-base disturbances, and after prolonged use of parenteral fluids which do not contain potassium.[25] An elevated serum potassium is seen in liver disease complicated by shock or uremia. Intracellular potassium is frequently low because of deficient protein and glycogen stores, dehydration, acid-base disturbances, and/or a deficient potassium intake. Total body potassium and its distribution may be determined by using dilution technics for compartment analysis, along with serum potassium and total exchangeable potassium.[26]

Mental Changes

Sensorial changes which include depression, somnolence, apathy, disorientation, agitation, delirium, and coma often develop in patients with impairment of hepatic function. Mental alterations are noted in one-half of patients with hepatic cirrhosis. They may be due to hepatic coma, delirium tremens, alcoholism, drugs, cerebrovascular disease, hypoglycemia, uremia, epilepsy, or functional psychoses.

Hepatic coma usually appears as a terminal event in liver disease. It must be differentiated from sensorial changes which accompany hypoglycemia, uremia, and drug intoxication. Serial study has not demonstrated any specific physical signs, biochemical function tests, or histology to account for the coma. Hepatic coma has been attributed to an accumulation of abnormal metabolites.[27] Laboratory studies show a normal cerebrospinal-fluid pressure, increased spinal-fluid protein, low serum electrolytes, and increased organic acids (pyruvic, ketoglutamic, and lactic) in many of these patients. An elevation of serum ammonium is often present. The elevated ammonium level is due to a lack of conversion of ammonia into urea[28] because of shunting of blood past the liver or marked hepatic dysfunction. It has been suggested that this elevation is responsible for mental changes; however, there may be an increased serum-ammonium level without cerebral dysfunction, and sensorial abnormalities are noted in the

presence of a normal serum ammonium. Furthermore, there is a marked variation in serum ammonium depending on the time allowed to lapse after blood is drawn for chemical study.[29] Sensorial changes accompanied by an elevation of serum ammonium occur in patients with hepatic disease who receive ammonium salts or resins,[30] and following protein feeding in patients with naturally occurring or surgically induced portacaval shunts.

Histologic study may show evidence of brain atrophy or hemorrhagic encephalopathy; in most instances, however, no morphologic lesion is present to account for mental alterations. Hepatic coma is precipitated by many distinct situations, including hemorrhage, infection, depressant drugs, and electrolyte disturbances. These factors appear to serve as trigger mechanisms. Mild to moderate hemorrhage, a single dose of a barbiturate or morphine, or a viral respiratory infection are often followed by coma in patients with

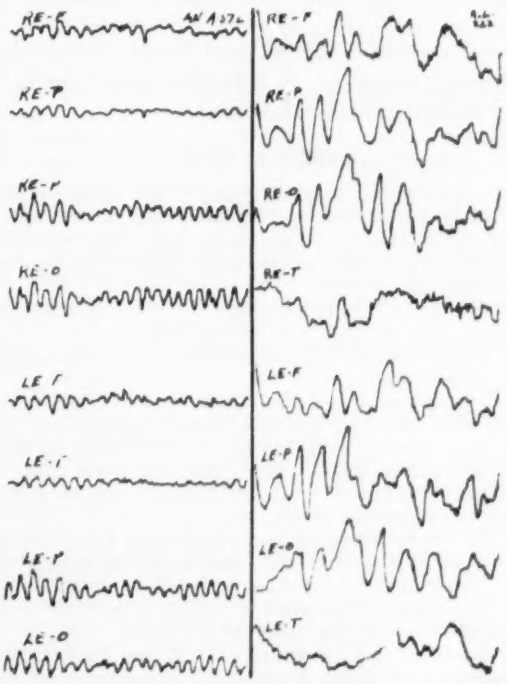

Fig. 3. **Electroencephalogram in hepatic coma (*left*), compared with normal tracing (*right*).**

severe hepatic insufficiency, whereas no adverse response is noted in patients with compensated liver disease.

Impending Hepatic Coma

Impending hepatic coma is characterized by pronounced slowing of normal mental processes, disorientation, and confusion. In the initial phases drowsiness and lethargy, or restlessness and agitation, are present. A "flapping" tremor is noted when the patient holds his arms forward with hands and fingers extended for a short period. It is characterized by coarse, irregular, flexion-extension movements of the fingers and wrists. Occasionally the lower extremities and facial area are involved. These tremors are accompanied by hyperactive reflexes and may be followed by bilateral extensor plantar responses. Electroencephalographic tracings show bilateral synchromous slow waves of two to three per second, most marked in the frontal area (Fig. 3). Triphasic waves appear when coma supervenes.[31]

(*Part III will include* Metabolic and Renal Abnormalities, Hematologic Syndromes, Reactions to Infections and Surgery, Neurologic Changes, and Subclinical Liver Disease.)

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